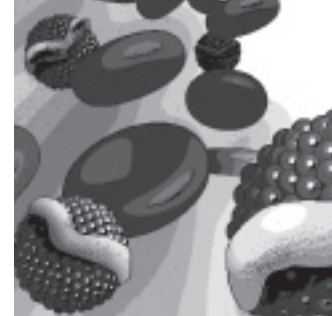


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Maternal lipid metabolism during normal pregnancy and its implications to fetal development

Whereas accumulation of fat depots occurs during the first two-thirds of gestation, increased adipose tissue lipolysis and hyperlipidemia develops in the last trimester. Insulin resistance and increased estrogens in late pregnancy contribute to these changes. Lipoprotein receptors and fatty acid binding proteins in the placenta allow the transfer of long-chain polyunsaturated fatty acids to the fetus. Enhanced oxidative stress in pregnancy may be related to maternal hyperlipidemia. Maternal plasma nonesterified fatty acids and cholesterol correlate with those in the fetus, and maternal adipocytokines have been associated with fetal growth. However, positive correlations between maternal nonesterified fatty acids or triacylglycerols and neonatal body weight or fat mass have only been found in gestational diabetics. Under the limited capacity of the fetus to modify the structure of essential polyunsaturated fatty acids, their long-chain derivatives have to be transferred from the mother through the placenta in appropriate amounts to warrant the normal fetal development.

KEYWORDS: adipose tissue ■ fat mass ■ fetus ■ hyperlipidemia ■ neonatal weight ■ oxidative stress ■ placenta

Fetal growth depends on maternal metabolic factors [1], glucose being the substrate, which crosses the placenta in greatest quantities and is used as the principal oxidative substrate by the fetus. Although a relationship between maternal plasma glucose levels and fetal growth has been found in both healthy [2] and diabetic women [3–6], there are also reports where no such correlation has been found [7,8] indicating that other factors besides the availability of glucose actively contribute to fetal growth. Alternatively, although lipids cross the placental barrier with difficulty [9], changes in lipid metabolism taking place on the maternal side could also contribute to fetal development and it has been reported that maternal triacylglycerols (TAG) and non-esterified fatty acids (NEFA) correlate with cord blood lipids and fetal growth [10–12].

Lipid metabolism greatly changes during physiologic pregnancy [13,14], but the way in which these changes affect lipid deposition in the adipose tissue of the fetus and its subsequent growth is not completely understood. The availability of substrates in the fetus depends on their concentration in the maternal circulation and to the extent they are transported across the placenta. Thus, maternal hyperlipidemia during pregnancy facilitates the availability of lipids to the fetus and could also contribute to its

accumulation in fat depots, as suggested by the correlations found between maternal NEFA and TAG close to delivery versus cord blood lipids and neonatal weight and fat mass, in well-controlled gestational diabetic (GDM) women [12].

Oxidative stress is present in normal pregnancies [15,16] and could be the result of maternal hyperlipidemia. However, increments of oxidative stress indices over control values have been associated with altered pregnancy outcome, as has been shown in diabetes [17,18], preeclampsia [19,20] and intrauterine growth restriction (IUGR) [21]. Although there is no consensus on the pathophysiological events underlying oxidative stress in these conditions, it has been proposed that supplements with antioxidants during pregnancy may be beneficial for both the mother and her fetus.

On the basis of the importance of maternal lipids on fetal development, this article reviews major changes in lipid metabolism that occur during normal pregnancy and their implications in fetal development.

Maternal lipid metabolism in pregnancy

Maternal accumulation of fat depots [22] and hyperlipidemia [13] are the two principal changes in lipid metabolism that occur during pregnancy.

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Moreover, essential fatty acids (EFAs) and long-chain polyunsaturated fatty acids (LCPUFAs) are needed for fetal growth and development, and must be obtained from maternal circulation.

■ Maternal fat accumulation

The accumulation of fat in maternal depots occurs during the first two-thirds of gestation. Maternal hyperphagia [23] increases the availability of substrates, which together with higher insulin levels and even enhanced insulin sensitivity [24–26] during early pregnancy, results in enhanced lipogenesis [27]. A second factor that appears to contribute to the accumulation of fat depots during early pregnancy is the increased activity of adipose tissue lipoprotein lipase (LPL) [28,29]. This enzyme, anchored in its active form in the capillary endothelium of extrahepatic tissues, hydrolyzes TAG circulating in plasma in the form of TAG-rich lipoproteins (i.e., chylomicrons and VLDL), and the hydrolytic products, fatty acids and glycerol, are mostly taken up by the subjacent tissue [30]. In this way, LPL activity being a prerequisite for the uptake of fatty acids from circulating TAG by adipose tissue, its increase during early pregnancy would also contribute to the accumulation of lipids in maternal depots.

The increase in fat depot accumulation stops or even declines during the last third of gestation [22,31], as a consequence of both enhanced adipose tissue lipolytic activity (see later) and decreased adipose tissue LPL activity. It has been found in late pregnant women that postheparin LPL activity decreases during the third trimester of gestation [13], and studies in late pregnant rats found that such a change corresponded to a decrease in the activity of the enzyme in adipose tissue [32]. Thus, the anabolic condition present in adipose tissue during early pregnancy switches to a net breakdown of maternal lipids, which is coincident with the highest rate of fetal growth.

■ Adipose tissue metabolism during pregnancy

Figure 1A schematically summarizes the main changes taking place in maternal adipose tissue during early pregnancy, which are mainly the result of the enhanced insulin sensitivity that takes place at this stage.

From studies in rats, it is known that the antilipolytic action of insulin in adipose tissue is enhanced during early pregnancy [25], which is in line with the reported increase in insulin sensitivity that has been found in the first third of gestation in both women [24,26] and rats [33].

Another alteration that contributes to the anabolic changes present in adipose tissue during early pregnancy is the unique capacity of the tissue to reutilize intracellularly the glycerol released throughout lipolysis. Under normal conditions, the negligible glycerol kinase activity in adipose tissue impedes the utilization of glycerol for glycerol-3-phosphate synthesis and its use for the synthesis of TAG [34,35]. However, an increase in glycerol kinase activity and its subsequent capacity to metabolize glycerol has been found in rodents under conditions of hyperinsulinemia and enhanced fat accumulation, such as obesity [36–39]. More recently, it has been reported that the *in vitro* capacity of adipose tissue to take up not only glucose but also glycerol and to convert them into glyceride glycerol is significantly enhanced in 7-day pregnant rats compared with nonpregnant or late pregnant rats [40]. The lower lipolytic activity together with the augmented capacity of the tissue for the synthesis of glycerol-3-phosphate for TAG synthesis from both glucose and intracellular released glycerol results in a net intracellular accumulation of TAG. These changes combined with the enhanced lipogenesis and LPL activity controlling the hydrolysis of circulating TAG and uptake of its products (NEFA and glycerol) (**Figure 1A**), explains the enhanced accumulation of fat depots that occurs during the first part of pregnancy. Since all these pathways are stimulated by insulin, it is proposed that the enhanced insulin responsiveness [25] in the presence of an augmented response of the pancreatic β cells to the insulinotropic stimulus of glucose that has been found both in early pregnant women [26] and in rats [33] would be the principal driving force for the net fat depot accumulation at this stage of pregnancy.

The anabolic condition of adipose tissue during early pregnancy switches to a net catabolic condition during the last third of gestation, as shown by a higher adipose tissue lipolytic activity and lower LPL activity [41,42]. These changes taking place in maternal adipose tissue metabolism during late pregnancy have been schematically summarized in **Figure 1B**. The presence of high plasma levels of placental hormones known to have lipolytic effects (i.e., human placental lactogen), an augmented production of catecholamines secondary to maternal hypoglycemia [43] and the insulin-resistant condition present at this stage [44,45], appears to be responsible for the net breakdown of maternal fat depots, consistently causing increments in plasma NEFA and glycerol levels during the third trimester of pregnancy.

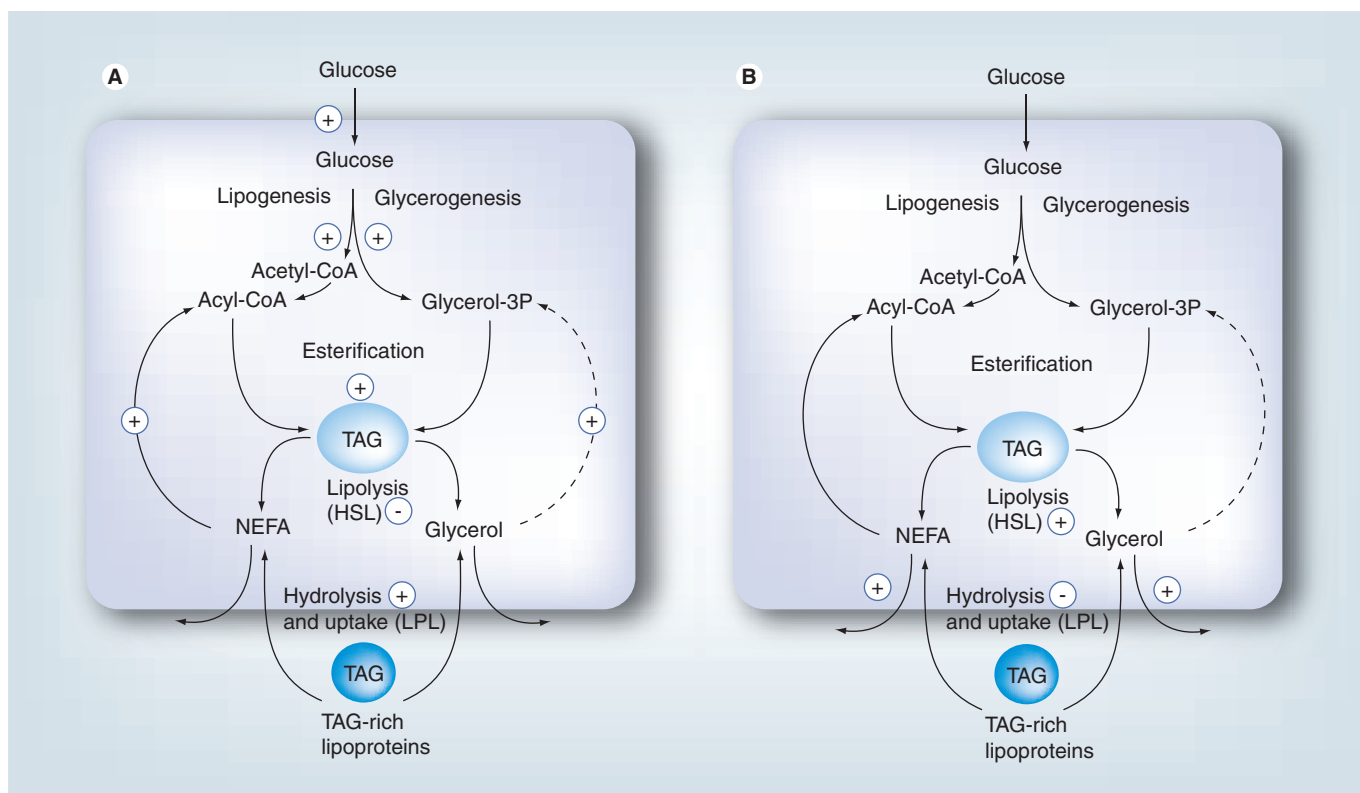


Figure 1. Adipose tissue metabolism during pregnancy. Schematic representation of the main changes taking place in maternal adipose tissue metabolism during early (A) and late pregnancy (B). Most of the proposed changes are driven by the changes in insulin sensitivity taking place during these two stages of pregnancy. + and – signs, respectively, indicate enhanced and decreased pathways. Additional details in the text.

NEFA: Nonesterified fatty acid; TAG: Triacylglycerol.

The main destination of these lipolytic products released from maternal adipose tissue is the maternal liver, where they are converted into their active forms, acyl-CoA and glycerol-3-phosphate, respectively, to become partially re-esterified for the synthesis of TAG, which are transferred to native VLDL particles and released into the circulation.

Besides the use of the active forms of lipolytic products in maternal liver for TAG synthesis, acyl-CoA can be converted throughout the β -oxidation pathway to acetyl-CoA, leading to energy production and ketone body synthesis, whereas glycerol may be used for glucose synthesis. These two pathways, ketogenesis and gluconeogenesis, increase markedly under fasting conditions in late pregnancy [46,47].

Since glucose is not only quantitatively the most abundant nutrient crossing the placenta [48,49], but is also the main oxidative substrate used by the fetus [50], the preferential use of glycerol released from maternal adipose tissue and reaching the maternal liver for gluconeogenesis acquires great importance during maternal fasting periods, when circulating

glucose levels are lower than under nonpregnant conditions [29]. Concerning the consumption of circulating ketone bodies, it is interesting to note that under fed conditions during early pregnancy, plasma ketone body values are even lower in pregnant than in nonpregnant conditions [51], which would indicate an enhanced use of these fuels by maternal tissues, probably as alternative substrates of glucose. However, during fasting conditions maternal ketogenesis becomes highly accelerated, as indicated by the exaggerated increase in plasma ketone bodies that occurs [51]. This condition benefits the fetus in two ways: first, ketone bodies are used by maternal tissues, thus saving glucose for essential functions and delivery to the fetus; and second, placental transfer of ketone bodies is very efficient, attaining the same concentration in fetal plasma as in maternal circulation [9]. In addition, ketone bodies may be used by the fetus as oxidative fuels as well as substrates for brain lipid synthesis [52].

The insulin-resistant condition present in late pregnancy seems to either play a key role in controlling these metabolic changes or is responsible for most of them. Insulin is well known to

inhibit adipose tissue lipolytic activity, hepatic gluconeogenesis and ketogenesis but to increase adipose tissue LPL activity. Thus, it is not surprising that all of these pathways change in the opposite direction to those stimulated by insulin during late pregnancy, when insulin resistance is consistently present. In fact, some of these pathways become even further modified under uncontrolled GDM conditions, where insulin resistance is further enhanced [14,24].

■ Maternal hyperlipidemia

The enhanced net breakdown of fat depots during late gestation is associated with hyperlipidemia, which chiefly corresponds to plasma rises in TAG, with smaller rises in phospholipids and cholesterol [53]. The greatest increase in plasma TAG corresponds to VLDL but they also accumulate in other lipoprotein fractions, which do not normally transport them, such as LDL and HDL, which are usually rich in esterified cholesterol and phospholipids, respectively [13]. The abundance of VLDL-TAG caused by their enhanced liver production [54] in the presence of an increase in cholesteryl ester transfer protein (CETP) activity, which takes place at midgestation [13,55], contributes to the accumulation of TAG in the lipoprotein fractions of higher densities, LDL and HDL [13,14]. This CETP facilitates the exchange of TAG by esterified cholesterol between VLDL and either LDL or HDL. Furthermore, it has been shown that during late pregnancy the activity of hepatic lipase (HL) greatly decreases [13], probably as a consequence of the well-known inhibitory action of estrogens on HL expression [56]. Thus, as summarized in **Figure 2**, the combined effect of enhanced liver production of VLDL [57,58], decreased removal of these particles from the circulation due to low LPL activity [13,59], high CETP activity and low HL activity, would not only be responsible for the accumulation of TAG in LDL but also for the proportional accumulation of TAG in buoyant TAG-rich HDL2b sub-fractions at the expense of the cholesterol-rich and TAG-poor HDL2a or HDL3 [13].

Placental transfer of lipids

■ Fatty acids

The supply of LCPUFA is important for fetal growth and tissue development, especially for the development of the nervous system. Both arachidonic acid (AA; 20:4 ω -6) and docosahexaenoic acid (DHA; 22:6 ω -3) are abundant in the brain and the retina and their appropriate supply during pregnancy and the neonatal period

is critical for proper function [60,61]. The importance of DHA in fetal development is indicated by the permanent impairment of retinal function and learning ability found under conditions of reduced accumulation of sufficient DHA during intrauterine life [60,61]. The importance of AA is mainly related to being a major component of structural phospholipids and serving as a precursor of eicosanoids, which play important roles in cell division, signal transduction and other physiologic processes. The critical role of AA in perinatal growth is evidenced by the association reported between its availability in preterm babies and birth weight and growth during the first year of life [62].

The two dietary EFA are linoleic acid (18:2 ω -6) and α -linolenic acid (18:3 ω -3), which are precursors of the ω -6 and ω -3 LCPUFA, respectively, by consecutive desaturation and chain elongation using the same enzyme system. Although EFA, as well as LCPUFA, are transferred across the placenta, the fetus needs to receive substantial amounts of preformed AA and DHA from maternal circulation to meet its tissue accretion rates. In the adult liver, AA and DHA can be synthesized to a limited extent from the EFA, but not in the fetus or the placenta, owing to the low activities of the desaturating enzymes. Therefore, the considerable requirements of these LCPUFA in the fetus must be provided by their placental transfer [63].

Most of the LCPUFA in maternal circulation are in their esterified form such as TAG, phospholipids and esterified cholesterol associated to plasma lipoproteins, with a lower proportion as NEFA [64]. Thus, although there is no direct placental transfer of maternal lipoproteins, as directly tested in rats [9] and suggested by the lack of lineal correlation between maternal and fetal plasma TAG correlation found in healthy women [HERRERA AND ORTEGA-SENOVILLA, UNPUBLISHED DATA], their LCPUFA must be available to the fetus. The placenta contains VLDL, LDL, HDL and scavenger receptors, as well as LDL receptor-related proteins. The placenta also has LPL, phospholipase A2 and intracellular lipase activities as well as plasma membrane fatty acid-binding protein (FABP/GOT2), fatty acid translocase (CD36), FATP and different cytoplasmic FABPs [9,64–66]. Thus, lipoproteins in maternal plasma can be taken up and handled by the placenta, allowing LCPUFA associated with plasma lipoproteins to be transferred to the fetus. The placental transfer of NEFA should also be efficient as suggested by the positive correlation found for this lipid

moiety between maternal and fetal plasma in women with moderate GDM [12]. Although the mechanisms by which those placental components facilitate the transfer of fatty acids to the fetus are not yet known, the process is very efficient. It permits the proportional enrichment in fetal plasma of certain LCPUFA such as AA and DHA, which decrease in maternal circulation [67] and which are essential for fetal development.

■ Cholesterol

The demand for cholesterol in the embryo and the fetus is relatively high. This is because cholesterol is an essential component of cell membranes, where it affects the fluidity and passive permeability and is the precursor of bile acids and steroid hormones. It is also required for cell proliferation and development of the growing body, cell differentiation and cell-to-cell communication, and is the precursor of oxysterols, which regulate key metabolic processes.

As reviewed previously [9], placental transfer of maternal cholesterol has been shown to be effective. However, cholesterol synthesis in fetal tissues, and especially in the fetal brain, has also been shown to be highly active, and the expression of the genes for the enzymes involved in cholesterol synthesis, as measured by mRNA content and by enzyme activity, is elevated in fetal tissues.

In humans, the comparison of maternal plasma concentrations of lipoprotein–cholesterol and those in umbilical cord blood gave positive correlations in some studies [68] but no correlation in others [69,70]. Gestational age seems to influence these comparisons, since in fetuses younger than 6 months, plasma cholesterol levels significantly correlate to the maternal ones [71], suggesting that, at these early stages of gestation, maternal cholesterol actively contributes to fetal cholesterol. Although it was generally assumed that during late pregnancy most of the fetal cholesterol is synthesized *de novo* by the fetus, present data in humans and animal models indicate that higher cholesterol availability on the maternal side substantially increases transfer [71–74]. Recently, the human term placental cholesterol transport mechanisms have been elucidated, establishing that placental endothelial cells are capable of transporting substantial amounts of cholesterol to the fetal circulation and that this mechanism is further enhanced by liver-X-receptors and induced upregulation of ATP-binding cassette transporters, ABCA1 and ABCG1 [75]. These findings and the positive correlation found in some studies between maternal

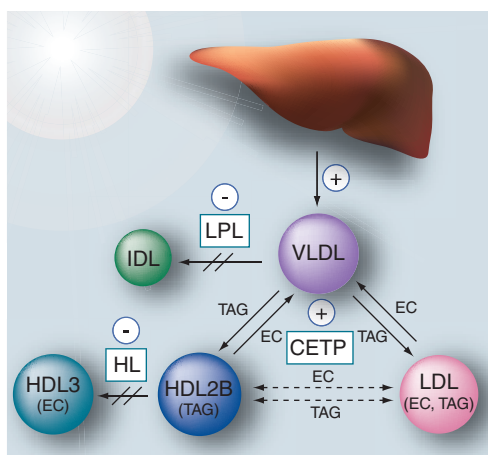


Figure 2. Lipoprotein metabolism during late pregnancy. Schematic representation of the mechanisms involved in the altered circulating lipoprotein profile during late pregnancy: + and – signs, respectively, indicate enhanced and decreased steps or enzyme activity.

CETP: Cholesteryl ester transfer protein; EC: Esterified cholesterol; HL: Hepatic lipase; LPL: Lipoprotein lipase; TAG: Triacylglycerol.

and cord blood cholesterol in women at term [68] indicate that although endogenous cholesterol synthesis may be an important source of fetal cholesterol, maternal–fetal cholesterol transfer is also effective, including at the end of gestation.

Implication of fatty acids in fetal development

Fatty acids are required by the developing fetus to maintain the fluidity, permeability and conformation of membranes, as a source of energy and as precursors of bioactive compounds such as eicosanoids. All fatty acids can act as energy sources but the structural and metabolic functions are performed largely by the LCPUFA [76]. Deposition of lipids in the fetus increases exponentially with gestational age, reaching an important accretion rate just before term [77]. Some of the fatty acids deposited in fetal adipose tissue (i.e., saturated and monounsaturated fatty acids) will accrue from fetal lipogenesis, but others are derived from maternal circulation via placental transfer. In this sense, an increase in levels of NEFA in maternal plasma at delivery, probably as a consequence of their lower placental transfer, has been found to be negatively associated with birth weight [70].

The nutritional status of the mother during gestation has been related to fetal growth and, in general, reduced dietary intake of ω -3 and ω -6 EFAs and/or their LCPUFA derivatives

has been correlated with reduced birth size in humans [78]. Significant linear correlations have been found between maternal and fetal levels of ω -3 and ω -6 fatty acids, and parallel increases in plasma DHA were found in the mothers and newborns after fish oil supplementation during pregnancy [79,80]. Owing to the importance of maternal dietary fatty acids in controlling the availability of PUFA to the fetus, strategies have been proposed to modify maternal intake of certain LCPUFA to account for their availability to the fetus; but an excess of certain fatty acids may impair the availability of others with undesirable consequences for newborns. The reason for this is the competitive desaturation of the ω -3 and ω -6 fatty acids by δ 6- and δ 5-desaturases, owing to their controlling role in the desaturating pathways of the parent EFA [81]. The inhibitory effect of both eicosapentanoic acid (C20:5 ω -3) and DHA on δ 5-desaturase activity is considered to be responsible for the lower plasma AA found when fish oil (high in eicosapentanoic acid and DHA) is consumed [81]. In addition, inhibition of δ 6-desaturase activity by fish oil has been demonstrated as being responsible for major declines in AA [82].

Apart from the overall placental supply of fatty acids, there is some evidence that the composition of certain fatty acids may also affect fetal growth. Decreased fetal AA content has been related to IUGR [83], low birth weight [62] and delayed postnatal development [84]. In addition, low fetal levels of AA could also be related to decreased growth during infancy [85,86]. However, there is no clear evidence of a deficiency of individual fatty acids in small for gestational age (SGA) or growth-restricted fetuses. Some researches have reported no differences in the AA:DHA ratio content of the cord blood in SGA fetuses [87], others reported significantly lower transplacental gradients in the ratios of AA and DHA [88], while others reported higher levels of DHA in placentas from growth-restricted fetuses [89].

All this suggests that it is possible to affect fetal growth by modifying the proportion of fatty acids in maternal circulation, which could be transferred throughout the placenta and not just their absolute amounts.

Oxidative stress in pregnancy

As previously described, one characteristic feature of normal gestation is the development of maternal hyperlipidemia. This hyperlipidemia during late pregnancy is associated with the

predominance of small and dense LDL particles [90], which have been shown to be more susceptible to oxidation [91]. The presence of these small LDL particles is compatible with the accumulation of TAG in maternal LDLs noted previously, since LDL represents a heterogeneous entity and both type of particles may be present in the same individual, this being specially the case under hyperlipidemic conditions. Hyperlipidemia and the occurrence of small and dense LDL particles during late pregnancy might increase oxidative damage. The oxidation processes are normally controlled by use of various scavenger antioxidant vitamins such as E, C and A, glutathione (GSH) and antioxidant enzymes such as superoxide dismutase, catalase, GSH peroxidase and GSH reductase. However, when there is an imbalance between free-radical production and the radical-scavenging capacity of the antioxidant systems, oxidative stress develops. There is evidence that oxidant species production is enhanced and antioxidant defences are disturbed during normal pregnancy [92]. Particular attention has been paid to the placenta, where lipid peroxidation products have been detected [93].

In late pregnancy, the higher levels of lipid peroxides are accompanied by higher levels of vitamin E [67], which appears to be responsible for the increase in the oxidative stability of LDL with progressing gestation [94]. In parallel to lipids, plasma levels of vitamin E significantly increase from the first trimester of gestation and reach a maximum in the third trimester [67]. Unlike vitamin A, there is no specific carrier protein in the serum to transport vitamin E, which circulates in its alcohol form in serum lipoproteins. Thus, changes in plasma vitamin E levels during pregnancy parallel maternal hyperlipidemia, in spite of which they are also accompanied by an increase in lipid peroxide production.

Vitamin E concentration in the plasma of human fetuses is lower than that found in their mothers, but rises towards the end of pregnancy. Since vitamin E is carried in plasma associated with the different lipoproteins, its uptake and handling by the placenta is similar to that of the other lipoprotein lipophilic components (see previous section). Furthermore, the placenta expresses α -tocopherol transfer protein and, similar to the role of this protein in liver, it may actively contribute to the specific transfer of vitamin E to the fetus [95]. In addition, owing to the need for fatty acid protection

against autoxidation in the fetus, the situation is more critical in early extrauterine life, when defense systems against reactive oxygen species are less well developed [96] and the newborn is suddenly submitted to increased oxygen concentrations. Thus, twice the amount of thiobarbituric acid reactivity has been found in neonatal red blood cells compared with adults [97], suggesting greater peroxidation damage in the former. The situation is further aggravated in premature infants with and without major clinical symptoms, who are born with adequate vitamin E levels according to their gestational age but which rapidly deplete if no appropriate vitamin E supplement is supplied [98]. GDM, chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis and retinopathy of prematurity are significant complications in premature infants whose etiologies have been associated with oxidative stress.

Therefore, during development, the fetus must have adequate antioxidant systems to guarantee maximum protection against oxidative processes to which it may be exposed.

Adipocytokines & fetal growth & development

A growing body of evidence has recently suggested that adipose tissue may play a major role in linking poor fetal growth to the subsequent development of adult diseases [99]. Insulin resistance, obesity-related diabetes and accompanying metabolic disorders are strongly associated with increased visceral fat mass [100]. Since the discovery of adipocyte-derived hormones, collectively termed adipocytokines, adipose tissue is no longer considered an inactive fat store tissue, but an endocrine organ, secreting a variety of bioactive molecules, which regulate body metabolism and energy homeostasis. Furthermore, adipocytokines have recently been implicated in fetal growth [101–103].

Leptin is the hormonal product of the obesity (*ob*) gene [104]. The central source of leptin is adipose tissue (white and brown), and during pregnancy, this hormone is produced in both maternal and fetal adipose tissue, although the decline in neonatal levels following birth may indicate the role of the placenta as an important contributor to fetal concentrations [105,106]. Serum leptin concentrations in maternal plasma are elevated throughout human pregnancy [107] and it increases substantially in the fetus after 34 weeks' gestation in relation to the rapid accumulation of body

fat mass during the latter half of the third trimester [108]. Circulating maternal leptin levels follow the overall major metabolic changes during the gestational period, including the anabolic to catabolic shift, and provide further evidence that leptin is one of the essential factors regulating the maternal and fetal energy balance [109]. Conversely, the dynamic of fetal leptin follows the evolution of fetal adipose tissue: the low fetal leptin levels during the first half of gestation increase dramatically during the last part of the third trimester [110,111]. Fetal leptin seems to play a role in overall fetal growth and development [109], and thus, different growth patterns *in utero* are accompanied by specific changes in leptin levels. For example, SGA infants have lower leptin at birth than appropriate for gestational age (AGA) children. However, large for gestational age neonates have high leptin levels [112]. Thus, leptin seems to be an important factor for fetal growth and development in addition to being necessary in the appropriate progression of the pregnancy.

Adiponectin is one of the most abundant adipocytokines and is predominantly expressed and secreted from adipose tissue [113]. It is thought that fetal adiponectin is mainly derived from fetal tissues and not from maternal tissues or the placenta [114]. Several lines of evidence support this notion. First, no correlation has been found between maternal adiponectin serum concentrations and adiponectin levels in cord blood. In addition, adiponectin levels in cord blood are significantly higher compared with maternal adiponectin levels and the possibility that the facilitated transport of adiponectin from the maternal blood through the placenta is responsible for the presence of high levels of the hormone in cord blood seems unlikely.

It has been claimed that adiponectin plays a role in the modulation of glucose and lipid metabolism in insulin-sensitive tissues [115]. Circulating adiponectin concentrations decrease in insulin-resistant states, including Type 2 diabetes [115,116]. Adiponectin may play a key role in fetal growth, probably enhancing the growth-promoting effect of insulin through its insulin-sensitizing action [117]. However, the relationship between fetal adiponectin and birth weight is not conclusive. Low concentration of adiponectin has been found in SGA newborns [102] but other studies did not find significant differences between SGA and AGA neonates [118,119]. Moreover, the lack of correlation between adiponectin and birth weight when adjusted

for gestational age [120,121] suggest that the latter has a greater effect than fetal weight on cord blood adiponectin levels. Recent studies have demonstrated that adiponectin secretion from omental but not from subcutaneous adipocytes is negatively correlated with the BMI in adults [122]. As newborns, and not adults, have predominantly subcutaneous adipose tissue, it could be that the lack of negative correlation between adiponectin in cord blood and birth weight is due to the different distribution of the adipose tissue depots.

Given the documented importance of fetal adipose tissue in fetal growth, the involvement of newly discovered adipocytokines in fetal growth is currently under investigation. Accordingly, resistin, RBP4, ghrelin, apelin and visfatin are some of the adipocytokines being studied as they are known to be involved or related to changes in insulin sensitivity, which might modulate fetal development. In the plasma of IUGR neonates compared with AGA, higher levels of ghrelin [123,124] and visfatin [125] and lower of RBP4 in SGA [118] have been reported. However, other studies have found no differences in resistin [126] and apelin between IUGR and AGA neonates [127], indicating little or no relationship between these factors and fetal growth. Owing to the well-established relationship between maternal weight gain and birth weight [128], endocrine factors derived from maternal and/or fetal adipose tissue would be expected to contribute to fetal growth, and therefore further studies are necessary in order to investigate the potential role of specific adipocytokines in fetal development.

Future perspective

Despite the ample knowledge that we already have on lipid metabolism during pregnancy, there are still a substantial number of open questions that are currently under research by several groups and will be clarified in the next 5–10 years. These questions mainly correspond to the intrinsic fetal lipid metabolism as well as the implications of maternal lipids under healthy or pathological conditions [129] on fetal development, as well as on its short- and long-term consequences in the health of adults.

The most relevant open questions relating to maternal lipid metabolism are discussed in the following section.

Maternal adipose tissue accumulation during early pregnancy may represent a store of essential lipid components derived from the maternal diet that may become mobilized during late

pregnancy, particularly under food-restricted conditions. Aside from the implications previously mentioned, if this were the case, accelerated breakdown of maternal adipose tissue during late pregnancy would represent a warranty for the availability of those essential lipid components to the fetus and the newborn. Even under normal nutritional conditions those essential components accumulated in maternal fat would be released around parturition to be taken up by the mammary glands and incorporated into the milk to become available to the suckling newborn. Although indirect studies carried out in sows support this possibility [130], well controlled studies in women and direct studies in animal models are clearly necessary.

Although most changes taking place in maternal lipoprotein metabolism that result in hyperlipidemia have been already elucidated, specific pathways need to be clarified. This is, for example, the case in the mechanism responsible for the preponderance of small dense LDL particles in the presence of TAG-rich LDL.

Another aspect that requires elucidation is the actual process of placental fatty acids transfer, and, in particular, PUFAs. Whereas most previous studies devoted to the determination of this process have been carried out under the assumption that maternal plasma NEFAs are the main source of fatty acids crossing the placenta, as commented previously in this article, most circulating PUFAs in the maternal circulation are in their esterified form associated to the different lipoprotein moieties. Although the placenta contains all the components that would allow the uptake and process of the different lipoprotein moieties, their cellular localization and actual contribution to the fatty acid transfer process is still far from being completed.

Besides the role of hormone changes and of the glucose and amino acids crossing the placenta, fetal development is greatly influenced by LCPUFA. From studies in adults, it is well known that some of these fatty acids are ligands of specific transcription factors and/or are substrates for key pathways (e.g., prostaglandins, in case of AA), but the mechanism of their contribution to fetal development remains to be elucidated.

Despite a substantial number of investigations currently being carried out, the influence of maternal and/or fetal adipocytokines on fetal development has not yet been clarified. On the basis of the significant correlations found between certain adipocytokines and fetal body

weight and/or fat mass, it is not yet possible to establish whether they are a consequence of their direct relationship or a reflection of some different endocrine- and growth-related processes. Additional research is clearly warranted in this specific field.

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Executive summary

Maternal fat accumulation

- The accumulation of fat depots during early pregnancy is induced by hyperinsulinemia and enhanced insulin sensitivity, increasing adipose tissue lipogenesis and lipoprotein lipase (LPL) activity.
- During the last trimester of gestation, an enhanced net fat depot breakdown is induced by insulin resistance.

Maternal adipose tissue metabolism & hyperlipidemia

- Enhanced lipolytic activity in maternal adipose tissue increases plasma nonesterified fatty acids and glycerol, whose principal destination is the maternal liver. Here, apart from being re-esterified for triacylglycerol (TAG) synthesis and released into the circulation associated to VLDL, they are used under fasting conditions for ketogenesis and gluconeogenesis.
- The combined effect of higher liver production of VLDL-TAG, lower LPL and hepatic lipase activities and higher cholesteryl ester transfer protein causes the accumulation of TAG in both LDL and HDL.

Placental transfer of lipids

- To develop, the fetus needs to obtain both essential fatty acids and long-chain polyunsaturated fatty acids derivatives (LCPUFAs) from the mother. These fatty acids are mainly carried in the maternal plasma in their esterified form associated with the different lipoproteins.
- Maternal lipoproteins do not cross the placenta directly, but the presence of receptors for all lipoproteins, lipase activities and fatty acid binding proteins allows for the efficient transfer of maternal LCPUFA to the fetus.
- Although endogenous cholesterol synthesis is an important source of fetal cholesterol, the placental endothelial cells are capable of transporting substantial amounts of cholesterol, and the positive lineal cholesterol correlation found in women at term between maternal and cord blood plasma indicate an efficient placental transfer of maternal cholesterol.

Long-chain polyunsaturated fatty acids play a key role in fetal development

- The quality and/or the quantity of maternal dietary fatty acids intake has been related to fetal growth.
- Significant lineal correlations between maternal and fetal level of ω -3 and ω -6 LCPUFA have been found.
- Both docosahexaenoic (22:6 ω -3) and arachidonic acid (20:4 ω -6) are essential fatty acids for fetal development, but an excess of either one could inhibit the availability of the other, due to their inhibitory effect on δ -5 and δ -6 desaturases.

Oxidative stress in pregnancy

- Hyperlipidemia and the occurrence of small and dense LDL particles in late pregnancy might increase oxidative damage. Higher levels of lipid peroxides are accompanied by higher levels of vitamin E, which parallel maternal hyperlipidemia.
- Lipid peroxidation products have been detected in the placenta, and the fetus needs to have adequate antioxidant systems to guarantee maximum protection against the oxidative process.

Adipocytokines & fetal growth

- Adipocyte-derived hormones (adipocytokines) have been implicated in fetal growth. In the fetus, serum leptin increases substantially during the final weeks of gestation in relation to the accumulation of body fat mass and it has been shown to be an important factor for fetal growth.
- Adiponectin is associated with insulin sensitivity. Although it has been postulated that it plays a key role in fetal growth, contradictory results found in intrauterine growth-restricted and small for gestational age neonates have failed to establish a relationship between fetal adiponectin and birth weight.
- The role of newly discovered adipocytokines in fetal growth are currently being investigated, since endocrine factors derived from maternal and/or fetal adipose tissue would be expected to contribute to fetal growth.

Conclusion

- Major changes in lipid metabolism take place during pregnancy. These are mainly controlled by the transition of enhanced insulin sensitivity during early pregnancy to the insulin resistance seen during the third trimester.
- Maternal hyperlipidemia during late pregnancy plays a key role in maternal metabolic adaptations that benefit fetal growth, particularly under conditions of dietary shortage.
- Lipids cross the placenta by means of complex mechanisms, and certain LCPUFAs from maternal circulation are essential for normal fetal development.
- Endocrine factors (i.e., adipocytokines) derived from maternal and/or fetal adipose tissue seems to play a key role in fetal growth, although their specific implications need to be investigated further.

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